```
      ---  -----  -----------
? s glutamic acid decarboxylase

      S1    1140  GLUTAMIC ACID DECARBOXYLASE
? s s1 and antisense

            1140  S1
           23939  ANTISENSE
      S2      12  S1 AND ANTISENSE
? rd

...completed examining records
      S3      12  RD (unique items)
? t s3/3,ab/all


 3/3,AB/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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12298470   BIOSIS NO.: 200000056337
Identification of a subpopulation of substantia nigra pars compacta
  gamma-aminobutyric acid neurons that is regulated by basal ganglia
  activity.
AUTHOR: Hebb M O; Robertson H A(a)
AUTHOR ADDRESS: (a)Laboratory of Molecular Neurobiology, Department of
  Pharmacology, Dalhousie University, Sir Charles Tupper Medical Building,
  Halifax, NS**Canada
JOURNAL: Journal of Comparative Neurology  416 (1):p30-44 Jan. 3, 2000
ISSN: 0021-9967
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In this report, the authors provide a novel description of a
  population of gamma-aminobutyric acid-containing neurons in the
  substantia nigra, pars compacta (SNC). By using metabolic mapping of the
  immediate-early gene, c-fos, the activation pattern of these cells was
  characterized with respect to basal ganglia stimulation. Dopaminergic
  stimulation with d-amphetamine or apomorphine induced Fos expression in
  the central region of the SNC. However, lesions of the nigrostriatal
  dopamine pathway significantly reduced d-amphetamine- and
  apomorphine-induced Fos expression in the ipsilateral and contralateral
  SNC, respectively. Suppression of stimulant-induced Fos expression in the
  striatum, using antisense oligodeoxynucleotides, also eliminated
  Fos expression in the ipsilateral SNC, indicating that striatal efferent
  projections are involved in the activation of these cells.
  Double-labeling immunohistochemistry revealed that the Fos-positive cells
  did not express tyrosine hydroxylase but were immunoreactive for glutamic
  acid decarboxylase. Retrograde labeling of nigrostriatal neurons,
  combined with Fos immunofluorescence, revealed that these Fos-positive
  cells did not project to the striatum. Thus, these neurons do not appear
  to comprise a nondopaminergic nigrostriatal circuit but likely represent
  locally-projecting interneurons of the substantia nigra.


 3/3,AB/2     (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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12291150 BIOSIS NO.: 200000049017
Autoimmune diabetes: Is GAD the culprit?
AUTHOR: Lopez-Liuchi Jose V(a)
AUTHOR ADDRESS: (a)Division d'Endocrinologie et Diabetologie, Departement de Medecine Interne, Hopital Universitaire de Geneve, Rue Micheli-du-Crest 24, 1211, Geneva 14**Switzerland
JOURNAL: European Journal of Endocrinology 141 (5):p458-459 Nov., 1999
ISSN: 0804-4643
DOCUMENT TYPE: Article
RECORD TYPE: Citation
LANGUAGE: English

3/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11993741 BIOSIS NO.: 199900274260
Control of autoimmune diabetes in NOD mice by GAD expression or suppression in beta cells.
AUTHOR: Yoon Ji-Won(a); Yoon Chang-Soon; Lim Hye-Won; Huang Qi Quan; Kang Yup; Pyun Kwang Ho; Hirasawa Kensuke; Sherwin Robert S; Jun Hee-Sook
AUTHOR ADDRESS: (a)Laboratory of Viral and Immunopathogenesis of Diabetes, Julia McFarlane Diabetes Research Centre**Canada
JOURNAL: Science (Washington D C) 284 (5417):p1183-1187 May 14, 1999
ISSN: 0036-8075
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Glutamic acid decarboxylase (GAD) is a pancreatic beta cell autoantigen in humans and nonobese diabetic (NOD) mice. beta Cell-specific suppression of GAD expression in two lines of **antisense** GAD transgenic NOD mice prevented autoimmune diabetes, whereas persistent GAD expression in the beta cells in the other four lines of **antisense** GAD transgenic NOD mice resulted in diabetes, similar to that seen in transgene-negative NOD mice. Complete suppression of beta cell GAD expression blocked the generation of diabetogenic T cells and protected islet grafts from autoimmune injury. Thus, beta cell-specific GAD expression is required for the development of autoimmune diabetes in NOD mice, and modulation of GAD might, therefore, have therapeutic value in type 1 diabetes.

3/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11966338 BIOSIS NO.: 199900219651
An increase in glutamate release follows a decrease in gamma aminobutyric acid and the pubertal increase in luteinizing hormone releasing hormone release in female rhesus monkeys.
AUTHOR: Terasawa E(a); Luchansky L L; Kasuya E; Nyberg C L
AUTHOR ADDRESS: (a)Wisconsin Regional Primate Research Center, 1223 Capitol Court, Madison, WI, 53715-1299**USA
JOURNAL: Journal of Neuroendocrinology 11 (4):p275-282 April, 1999
ISSN: 0953-8194
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Previously we have shown that release of gamma-aminobutyric acid (GABA) in the stalk-median eminence (S-ME) is high in prepubertal monkeys and that a decrease in GABA release triggers the onset of puberty. However, it is still unclear how disinhibition of the luteinizing hormone releasing hormone (LHRH) neuronal system from GABA input is followed (or accompanied) by an increase in stimulatory signals, such as glutamatergic input to LHRH neurons. To clarify the temporal relationship between the reduction of the GABAergic inhibitory signal and the enhancement of the glutamatergic stimulatory signal in the control of LHRH release at the onset of puberty, we conducted two experiments using a push-pull perfusion method. In the first experiment, we measured developmental changes in release of LHRH, GABA, and glutamate in the S-ME. LHRH levels were very low in prepubertal monkeys, increased to higher levels in early pubertal monkeys, with the highest LHRH levels occurring in mid-pubertal monkeys. As we previously observed, GABA levels were high in prepubertal monkeys and then decreased in early- and mid-pubertal monkeys. In contrast, glutamate levels were very low in prepubertal monkeys, increased dramatically in early pubertal monkeys, and then slightly decreased in mid-pubertal monkeys, although mid-pubertal levels remained much higher than prepubertal levels. In the second experiment, we measured GABA, glutamate and LHRH in the same samples obtained from prepubertal monkeys which were infused with an **antisense** oligodeoxynucleotide (AS) for glutamic acid decarboxylase (GAD) 67 mRNA into the S-ME. GAD67 is a catalytic enzyme for GABA synthesis from glutamate, and AS GAD67 mRNA interferes with GAD67 synthesis. Infusion of the AS GAD67 induced a decrease in GABA release, which subsequently resulted in an increase in LHRH release. Surprisingly, glutamate release also increased several hours after the decrease in GABA release, and the increased LHRH release continued. These data are interpreted to mean that a decrease in GABA synthesis by interference with GAD67 synthesis and the reduction of GABA release in the S-ME trigger an increase in LHRH release, but that a subsequent increase in glutamate release in the S-ME further contributes to the pubertal increase in LHRH release at the onset of puberty. The data further support our hypothesis that GAD plays an important role in the mechanism of the onset of puberty.

3/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11402445 BIOSIS NO.: 199800183777
Effect of injection of **antisense** oligodeoxynucleotides of GAD isozymes into rat ventromedial hypothalamus on food intake and locomotor activity.
AUTHOR: Bannai Makoto; Ichikawa Masumi; Nishihara Masugi; Takahashi Michio (a)
AUTHOR ADDRESS: (a)Dep. Vet. Physiol., Vet. Med. Sci., Univ. Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113**Japan
JOURNAL: Brain Research 784 (1-2):p305-315 Feb. 16, 1998
ISSN: 0006-8993
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In the ventromedial hypothalamus (VMH), gamma-aminobutyric acid (GABA) plays a role in regulating feeding and running behaviors. The GABA synthetic enzyme, glutamic acid decarboxylase (GAD), consists of two isozymes, GAD65 and GAD67. In the present study, the phosphorothioated **antisense** oligodeoxynucleotides (ODNs) of each GAD isozyme were injected bilaterally into the VMH of male rats, and food intake, body weight and locomotor activity were monitored. ODNs were incorporated in the water-absorbent polymer (WAP, 0.2 nmol/mul) so that ODNs were retained at the injection site. Each **antisense** ODN of GAD65 or GAD67 tended to reduce food intake on day 1 (day of injection = day 0)

though not significantly. An injection combining both **antisense** ODNs significantly decreased food intake only on day 1 but body weight remained significantly lower than the control for 5 days. This suppression of body weight gain could be attributed to a significant increase in locomotor activity between days 3 and 5. Individual treatment with either ODNs did not change locomotor activity. The increase in daily locomotor activity in the group receiving the combined **antisense** ODNs occurred mainly during the light phase. Neither vehicle (WAP) nor control ODN affected food intake, body weight and locomotor activity. Histological studies indicated that **antisense** ODN distributed within 800 mum from the edge of the area where WAP was located 24 h after the injection gradually disappeared within days, but still remained within 300 mum distance even 7 days after the injection. **Antisense** ODN was effectively incorporated by all the cell types examined, i.e., neurons, astrocytes and microglias. Further, HPLC analysis revealed that **antisense** ODNs of GAD isozymes, either alone or combined, decreased the content of GABA by 50% in VMH 24 h after the injection. These results indicate that suppression of GABA synthesis by either of the GAD isozymes is synergistically involved in suppressing food intake and enhancing locomotor activity in rat VMH.

3/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11212715 BIOSIS NO.: 199799833860
Antisense oligodeoxynucleotides to two isozymes of glutamic acid decarboxylase incorporated in HVJ-liposome and injected into rat VMH differentially modify food intake.
AUTHOR: Bannai M(a); Kaneda Y; Ichikawa M; Nishihara M; Takahashi M
AUTHOR ADDRESS: (a)Dep. Vet. Physiol., Univ. Tokyo, Tokyo 113**Japan
JOURNAL: Society for Neuroscience Abstracts 23 (1-2):p2378 1997
CONFERENCE/MEETING: 27th Annual Meeting of the Society for Neuroscience New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English

3/3,AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11208174 BIOSIS NO.: 199799829319
Effects of infusions of **antisense** oligonucleotides for glutamic acid decarboxylase into the nucleus accumbens on behavioral vigilance.
AUTHOR: Miner L A H; Sarter M
AUTHOR ADDRESS: Dep. Psychol. Neurosci. Program, Ohio State Univ., Columbus, OH 43210**USA
JOURNAL: Society for Neuroscience Abstracts 23 (1-2):p1600 1997
CONFERENCE/MEETING: 27th Annual Meeting of the Society for Neuroscience New Orleans, Louisiana, USA October 25-30, 1997
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English

3/3,AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10340599 BIOSIS NO.: 199698795517
Role of glutamic acid decarboxylase in the prepubertal inhibition of the luteinizing hormone releasing hormone release in female rhesus monkeys.

AUTHOR: Mitsushima Dai; [redacted]rzban Farshid; Luchansky Laure [redacted]; Burich Andrew J ; Keen Kim L; Durning [redacted]reen; Golos Thaddeus G; Teras[redacted] Ei(a)
AUTHOR ADDRESS: (a)Wisconsin Regional Primate Res. Cent., 1223 Capitol Court, Madison, WI 53715**USA
JOURNAL: Journal of Neuroscience 16 (8):p2563-2573 1996
ISSN: 0270-6474
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To investigate further the role of GABA in the onset of puberty, this study examines whether glutamic acid decarboxylase (GAD), the catalytic enzyme for GABA synthesis, is involved in the suppression of luteinizing hormone releasing hormone (LHRH) before puberty in rhesus monkeys. First, both GAD67 and GAD65 mRNAs were detectable by reverse transcription-PCR analysis in the preoptic area, medio-basal hypothalamus, posterior hypothalamic area, and hippocampus of the monkey brain. Second, effects of **antisense** oligodeoxynucleotides (D-oligos) for GAD67 and GAD65 mRNAs on LHRH release were examined in conscious female rhesus monkeys at the prepubertal stage using a push-pull perfusion method. The GAD67 or GAD65 **antisense** D-oligos or scrambled D-oligos were infused directly into the stalk-median eminence. Both the GAD67 and the GAD65 **antisense** D-Oligos induced a large and prompt increase in LHRH release, whereas the scrambled D-oligos did not induce any significant effect. The results suggest that the removal of GABA inhibition by interfering with GAD synthesis is effective in increasing LHRH release in prepubertal monkeys. Third, the specificity of the **antisense** D-oligos on GAD levels was examined by incubating basal hypothalami with D-oligos in vitro and subsequent Western blot analysis. The **antisense** D-oligos consistently decreased the proteins GAD67 and GAD65 compared with respective control D-oligos. We conclude that the decrease of tonic GABAergic inhibition and maturational changes in GAD synthesis may be critical factors for the onset of puberty in nonhuman primates.

3/3,AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10074455 BIOSIS NO.: 199598529373
Antisense oligonucleotide modulation of GAD alters cocaine-induced seizures in mice.
AUTHOR: Abel M S; Kirages T J
AUTHOR ADDRESS: Dep. Cell Biol. Anatomy, FUHS/Chicago Medical School, Chicago, IL 60064**USA
JOURNAL: Society for Neuroscience Abstracts 21 (1-3):p1592 1995
CONFERENCE/MEETING: 25th Annual Meeting of the Society for Neuroscience San Diego, California, USA November 11-16, 1995
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English

3/3,AB/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09168808 BIOSIS NO.: 199497177178
Intracerebral administration of **antisense** oligodeoxynucleotides to GAD-65 and GAD-67 mRNAs modulate reproductive behavior in the female rat.
AUTHOR: McCarthy Margaret M(a); Masters David B; Rimvall Karin; Schwartz-Giblin Susan; Pfaff Donald W
AUTHOR ADDRESS: (a)Dep. Physiol., Univ. Md.-Sch. Med., 655 West Baltimore St., Baltimore, MD 20201-1559**USA

JOURNAL: Brain Research 636 (2):p209-220 1994
ISSN: 0006-8993
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Increased GABA activity in the medial hypothalamus (HYP) and midbrain central gray (MCG), but not the preoptic area (POA), facilitates sexual receptivity in the female rat (40). In the current experiments, ovariectomized females were chronically treated with estrogen (via silastic capsules) to maintain a continuously high level of lordosis response. Administration of crystalline **antisense** oligodeoxynucleotide to the GABA synthetic enzyme, GAD-67, into the HYP and MCG significantly and reversibly reduced lordosis response for 1-2 days, but did not inhibit lordosis when administered into the POA. Administration of a control oligonucleotide, consisting of the same nucleotide bases but in a scrambled sequence, did not significantly modulate behavior when infused into any brain areas. When oligodeoxynucleotide **antisense** to GAD-67 was suspended in oil and then infused into the HYP or MCG it was more effective and resulted in less inter-animal variability. Subsequent experiments involving infusions into the MCG compared the effectiveness of **antisense** oligonucleotides to the two different forms of GAD, known as GAD-65 and GAD-67. Oligodeoxynucleotides **antisense** to the mRNA for either gene were effective at reducing lordosis behavior but with a different time course. Oligonucleotide **antisense** to GAD-67 significantly reduced behavior within 24 h of infusion and there was full recovery by 4 days post-infusion. GAD-65 **antisense** oligonucleotide did not significantly reduce behavior until 48 h post infusion and animals did not fully recover to pretest levels of lordosis until 5 days post-infusion. When **antisense** oligonucleotide for the two genes was administered simultaneously, the inhibition of lordosis was maximal at 24 h and stayed depressed for 4 days. There did not appear to be an additive effect of the two different **antisense** oligonucleotides when administered together. Tissue GABA levels in HYP and MCG of individual rats assayed by HPLC were no longer correlated with lordosis score after **antisense** oligonucleotide infusion but were after infusions of scrambled control oligos. Immunoblotting for the two forms of GAD revealed that GAD-67 **antisense** oligonucleotide infusion led to significant decreases in both GAD-67 and GAD-65 protein levels as compared to infusions of scrambled control oligo. In addition, the levels of a neuronal marker, neuron-specific enolase, also decreased (although nonsignificantly) suggesting either a temporary shutdown of protein synthesis or a degeneration of GABAergic neurons after GAD-67 **antisense** oligonucleotide infusion.

3/3,AB/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09040654 BIOSIS NO.: 199497049024
Glutamic acid decarboxylase gene expression in thalamic reticular neurons transplanted as a cell suspension in the adult thalamus.
AUTHOR: Nothias Fatiha; Salin Pascal; Peschanski Marc; Chesselet Marie-Francoise(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol., University Pennsylvania, 36th St. and Hamilton Walk, Philadelphia, PA 19104**USA
JOURNAL: Molecular Brain Research 20 (3):p245-253 1993
ISSN: 0169-328X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The goal of the present study was to determine whether

alterations in neuronal morphology and connections in thalamic grafts were accompanied by changes in the expression of mRNA encoding glutamic acid decarboxylase (GAD), the key enzyme in the synthesis of GABA, the normal neurotransmitter of neurons of the thalamic reticular nucleus. Cell suspensions of rat fetal tissue containing both thalamic reticular nucleus and ventrobasal primordia were transplanted into the excitotoxically lesioned somatosensory thalamus of adult rats. Levels of messenger RNA (mRNA) encoding GAD (Mr 67,000; GAD67) were measured 7 days to 4 months following transplantation via quantitative in situ hybridization with 35S-radiolabeled **antisense** RNAs. Expression of GAD67 mRNA in the thalamic reticular nucleus was analyzed in parallel in rat pups between 0 and 30 days postnatally, and in adult animals. As already observed with immunohistochemistry, transplanted neurons of the thalamic reticular nucleus did not group in specific clusters but rather mingled with unlabeled (putatively ventrobasal) neurons. Levels of labelling for GAD67 mRNA per neuron increased over time and reached adult levels during the third week post-grafting, i.e. 2 weeks after the theoretical birthdate of the neurons (grafted at embryonic days 15-16). Similar values were observed and a plateau was reached at similar time points during normal ontogeny. The results suggest that, in contrast to morphology and size of the neuronal cell bodies, gene expression of GAD67 develops normally despite the ectopic location of neurons of the thalamic reticular nucleus in the somatosensory thalamus, the abnormal connectivity and the lack of segregation from non-GABAergic neurons. Therefore, dissociation and transplantation of the tissue, resulting in disruption of the extracellular matrix and alteration of cellular interactions, differentially affects various aspects of neuronal maturation. Because neuronal activity in the graft is similar to that in the adult thalamic reticular nucleus, the results further suggest that, as shown in other experimental systems, GAD67 mRNA levels in the graft are regulated in relation to the functional activity of GABAergic neurons.

3/3,AB/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09010907 BIOSIS NO.: 199497019277
Direct infusion of a glutamic acid decarboxylase (GAD1) **antisense** oligodeoxynucleotide into the stalk-median eminence (S-ME) increases the in vivo LHRH release in prepubertal female monkeys.
AUTHOR: Mitsushima D; Marzban F; Hei D L; Golos T G; Terasawa E
AUTHOR ADDRESS: Wis. Regional Primate Res. Cent., Univ. Wis., Madison, WI 53715**USA
JOURNAL: Society for Neuroscience Abstracts 19 (1-3):p618 1993
CONFERENCE/MEETING: 23rd Annual Meeting of the Society for Neuroscience Washington, D.C., USA November 7-12, 1993
ISSN: 0190-5295
RECORD TYPE: Citation

```
? s glutamate and receptor and antisense

          97300  GLUTAMATE
         743580  RECEPTOR
          23939  ANTISENSE
     S4     117  GLUTAMATE AND RECEPTOR AND ANTISENSE
? rd

...examined 50 records  (50)
...examined 50 records  (100)
...completed examining records
     S5      83  RD (unique items)
? s s5 and parkinson

             83  S5
          46501  PARKINSON
     S6       0  S5 AND PARKINSON
? s s5 and parkinson?

             83  S5
          55750  PARKINSON?
     S7       0  S5 AND PARKINSON?
? s s5 and nigra

             83  S5
          29402  NIGRA
     S8       0  S5 AND NIGRA
? s s5 and globus

             83  S5
           8670  GLOBUS
     S9       0  S5 AND GLOBUS
? s s5 and gaba

             83  S5
          61057  GABA
    S10       6  S5 AND GABA
? s gaba and receptor and antisense

          61057  GABA
         743580  RECEPTOR
          23939  ANTISENSE
    S11     113  GABA AND RECEPTOR AND ANTISENSE
? s s1 not s10

           1140  S1
              6  S10
    S12    1140  S1 NOT S10
? s s11 not s10

            113  S11
              6  S10
    S13     107  S11 NOT S10
? rd

...examined 50 records  (50)
...examined 50 records  (100)
...completed examining records
    S14      76  RD (unique items)
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? s s14 and parkinson?

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            76  S14
         55750  PARKINSON?
    S15       1  S14 AND PARKINSON?
? s s15 or s10

             1  S15
             6  S10
    S16      7  S15 OR S10
? t s16/3,ab/all
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16/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10081986 99350600

Glutamatergic synaptic responses and long-term potentiation are impaired in the CA1 hippocampal area of calbindin D(28k)-deficient mice.

Jouvenceau A; Potier B; Battini R; Ferrari S; Dutar P; Billard JM
Laboratoire de Physiopharmacologie du Systeme Nerveux, Paris, France.

Synapse (UNITED STATES) Sep 1 1999, 33 (3) p172-80, ISSN 0887-4476
Journal Code: VFL
Languages: ENGLISH
Document type: JOURNAL ARTICLE

The contribution of the cytosolic calcium binding protein calbindin D(28K) (CaBP) to glutamatergic neurotransmission and synaptic plasticity was investigated in hippocampal CA1 area of wild-type and **antisense** transgenic CaBP-deficient mice, with the use of extracellular recordings in the ex vivo slice preparation. The amplitude of non-N-methyl-D-aspartate **receptor** (non-NMDAr)-mediated extracellular field excitatory postsynaptic potentials (fEPSPs) recorded in control medium was significantly greater in CaBP-deficient mice, whereas the afferent fiber volley was not affected. In contrast, the amplitude of NMDAr-mediated fEPSPs isolated in a magnesium-free medium after blockade of non-NMDAr and GABAergic receptors was significantly depressed in these animals. No alteration in the magnitude of paired-pulse facilitation was found, indicating that the presynaptic calcium mechanisms controlling **glutamate** release were not altered in CaBP-deficient mice. The magnitude and time course of the short-term potentiation (STP) of fEPSPs induced by a 30 Hz conditioning stimulation, which was blocked by the NMDAr antagonist 2-amino-5-phosphonovalerate acid (2-APV), was not impaired in the transgenic mice, whereas long-term potentiation (LTP) induced by a 100 Hz tetanus was not maintained. The long-term depression (LTD) induced by low-frequency stimulation (1 Hz, 15 min) in the presence of the **GABA** antagonist bicuculline was not altered. These results argue for a contribution of CaBP to the mechanisms responsible for the maintenance of long-term synaptic potentiation, at least in part by modulating the activation of NMDA receptors. Copyright 1999 Wiley-Liss, Inc.

16/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09875101 99079264

Functional neuroanatomy of the basal ganglia as studied by dual-probe microdialysis.

O'Connor WT
Department of Human Anatomy and Physiology, University College, Dublin, Ireland. woconn@iveagh.ucd.ie

Nucl Med Biol (ENGLAND) Nov 1998, 25 (8) p743-6, ISSN 0969-8051
Journal Code: BOO
Languages: ENGLISH

Document type: JOURNAL ARTICLE
Dual probe microdialysis was employed in intact rat brain to investigate the effect of intrastriatal perfusion with selective dopamine D1 and D2 **receptor** agonists and with c-fos **antisense** oligonucleotide on (a) local **GABA** release in the striatum; (b) the internal segment of the globus pallidus and the substantia nigra pars reticulata, which is the output site of the strionigral **GABA** pathway; and (c) the external segment of the globus pallidus, which is the output site of the striopallidal **GABA** pathway. The data provide functional in vivo evidence for a selective dopamine D1 **receptor**-mediated activation of the direct strionigral **GABA** pathway and a selective dopamine D2 **receptor** inhibition of the indirect striopallidal **GABA** pathway and provides a neuronal substrate for parallel processing in the basal ganglia regulation of motor function. Taken together, these findings offer new therapeutic strategies for the treatment of dopamine-linked disorders such as **Parkinson**'s disease, Huntington's disease, and schizophrenia.

16/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09841607 99124487
A role of gamma-amino butyric acid (**GABA**) and **glutamate** in control of puberty in female rhesus monkeys: effect of an **antisense** oligodeoxynucleotide for GAD67 messenger ribonucleic acid and MK801 on luteinizing hormone-releasing hormone release.
Kasuya E; Nyberg CL; Mogi K; Terasawa E
Wisconsin Regional Primate Research Center, University of Wisconsin-Madison, 53715-1299, USA.
Endocrinology (UNITED STATES) Feb 1999, 140 (2) p705-12, ISSN 0013-7227 Journal Code: EGZ
Contract/Grant No.: HD-11355, HD, NICHD; HD-15433, HD, NICHD; RR-00167, RR, NCRR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previously we have shown that gamma-aminobutyric acid (**GABA**) is an inhibitory neurotransmitter restricting the pubertal increase in LHRH release in juvenile monkeys, and that interfering with **GABA** synthesis with an **antisense** oligodeoxynucleotide (AS) for glutamic acid decarboxylase (GAD67) mRNA results in an increase in LHRH release in prepubertal monkeys. GAD67 is a catalytic enzyme that synthesizes **GABA** from **glutamate**. To further clarify the role of **GABA** in puberty, we examined whether the inhibition of LHRH release by **GABA** continues after the onset of puberty and whether input from glutamatergic neurons plays any role in the onset of puberty when **GABA** inhibition declines, using a push-pull perfusion method. In Study I, the effects of the AS GAD67 mRNA on LHRH release in pubertal monkeys (34.3 +/- 1.5 months of age, n = 8) were examined, and the results were compared with those in prepubertal monkeys (18.5 +/- 0.4 months, n = 12). Direct infusion of AS GAD67 (1 microM) into the stalk-median eminence (S-ME) for 5 h stimulated LHRH release in both prepubertal and pubertal monkeys. However, the increase in LHRH release in pubertal monkeys was significantly ($P < 0.01$) smaller than that in prepubertal monkeys. Infusion of a scrambled oligo as a control was without effect in either group. In Study II, to examine the possibility that an increase in **glutamate** tone after the reduction of an inhibitory **GABA** tone contributes to the AS GAD67-induced LHRH increase, the effects of the NMDA **receptor** blocker MK801 (5 microM) on LHRH release were tested in monkeys treated with AS GAD67. MK801 infusion into the S-ME during the treatment of AS GAD67 (1 microM) suppressed the AS GAD67-induced LHRH release in both age groups. MK801 alone did not cause any significant effect in either group. The data are interpreted to mean that **GABA** continues to suppress LHRH release after the onset of puberty, although the degree of suppression is weakened considerably after the onset of puberty, and that the increased

LHRH release after AS GAD67 treatment may be partly due to an increase in **glutamate** tone mediated by NMDA receptors, as well as due to the decrease in **GABA** release following the decrease in GAD synthesis. Taken together, the present results suggest that GAD may play an important role in the onset and progress of puberty in nonhuman primates.

16/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08898046 96233196
Cocaine selectively alters neurotransmitter **receptor** mRNAs in mouse embryos.
Mackler SA; Bennett GD; Tsuei VP; Finnell RH
Division of General Internal Medicine, University of Pennsylvania, Philadelphia, USA.
Reprod Toxicol (UNITED STATES) Jan-Feb 1996, 10 (1) p37-42, ISSN 0890-6238 Journal Code: BE4
Contract/Grant No.: ES07165, ES, NIEHS; DE11303, DE, NIDR; DA00199, DA, NIDA
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Alterations in gene expression due to in utero cocaine exposure may adversely affect nervous system development. The present study examined whether or not cocaine administration to pregnant mice alters embryonic mRNA levels for several developmentally-regulated genes. **Antisense** RNA amplification was performed using RNA from LM/Bc embryos at gestational days 9.5 and 10.5 after three days of cocaine treatment. This technique highlights simultaneous changes that occur in the expression of many genes after a teratogenic insult. Significant changes occurred in the expression pattern on only four genes from a total of 42 candidate cDNAs. These included increases in the relative levels of the alpha and beta 1 subunits of the GABAA **receptor** without concurrent changes in the non-NMDA **glutamate receptor** subunits. The results support the hypothesis that in utero cocaine exposure leads to specific changes in gene expression that may ultimately contribute to developmental abnormalities.

16/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08400577 95388262
Antisense oligonucleotide-induced block of individual GABAA **receptor** alpha subunits in cultured visual cortex slices reduces amplitude of evoked inhibitory postsynaptic currents.
Brussaard AB; Baker RE
Graduate School Neurosciences Amsterdam, Research Institute Neurosciences, Vrije Universiteit, Faculty of Biology, The Netherlands.
Neurosci Lett (IRELAND) May 19 1995, 191 (1-2) p111-5, ISSN 0304-3940 Journal Code: N7N
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Whole cell patch clamp recordings were made in layer II-IV from organotypic slices of rat primary visual cortex, explanted at postnatal day 6 and maintained in a serum-free medium. Neurons evinced current clamp characteristics typical for stellate cells. Between 7 and 21 days in culture, both **glutamate**- and **GABA** -mediated postsynaptic currents were observed. Long-term culturing in the presence of a degenerate 15-mer **antisense** oligonucleotide directed against the transcripts of all alpha subunits genes of the GABAA **receptor** resulted in a dose dependent reduction of evoked **GABA** synaptic currents. This reduction was maximal (80%) at 20 microM. A randomized control oligo had no effect. Evoked glutamatergic excitatory postsynaptic currents were unaffected

following oligo treatment. A 15-mer **antisense** oligo directed against the alpha 1 subunit gave variable effects: in some cells the amplitude of evoked GABAergic inhibitory postsynaptic currents (IPSCs) was reduced by 50-75%, while in other cells recorded from the same slices, there was little or no effect. An **antisense** oligo, directed against the alpha 2 subunit, however, gave a consistent and robust 80% reduction of the amplitude of evoked IPSCs. A 15-mer 3-base mismatch oligo against alpha 2 had no effect. We conclude that the alpha 2 subunit functions in postsynaptic GABAA receptors located on or close to the cell bodies of stellate cells. The role of the alpha 1 subunit is less clear, but this subunit seems spatially differentiated. The in situ **antisense** oligo technique should provide further insight into the biophysical and pharmacological consequences of the subunit composition of ligand gated channels at functional synapses.

16/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07293308 93148187
Building a bridge between neurobiology and mental illness.
Costa E
Fidia-Georgetown Institute for the Neurosciences, Georgetown University Medical School, Washington, DC 20007.
J Psychiatr Res (ENGLAND) Oct 1992, 26 (4) p449-60, ISSN 0022-3956 Journal Code: JTJ
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
GABA (gamma amino butyric acid) is the most abundant and important inhibitory transmitter in mammalian CNS. It counterbalances the **glutamate** mediated neuronal excitation. Abnormalities of the interaction of these two transmitters might change the mechanisms of neuronal group selection that according to Edelman [Neural Darwinism. Basic Books, New York] play a role in mediating several brain functions including cognition processes. Indeed imbalances in GABAergic functions were shown to elicit psychoses. They can be obtained by administration of drugs that affect synthesis, metabolism and uptake of **GABA** and thereby cause a persistent stimulation of GABAA receptors or perhaps by genetic abnormalities in DNA transcription, pre-mRNA splicing, mRNA translation and posttranslation modifications of GABAA **receptor** subunits. The complexities in the regulation of GABAA **receptor** subunit structure, synthesis, assembly and the brain location of specific mRNA encoding for these subunits are investigated with in situ mRNA hybridization specific for subunits of GABAA receptors. The role of the variability resulting from the complexities in the regulation of GABAA **receptor** allosteric modulation by drugs and putative endogenous allosteric modulators of **GABA** action at GABAA receptors is discussed. This discussion gives relevance to the possibility that genetic abnormalities in the expression of proteins participating in GABAergic function are to be considered as a possible target of the genetic defects operative in psychoses. In line with this thinking, it is suggested that partial allosteric modulators (partial agonists) of GABAA receptors and the phosphothioate or methylphosphonate analogs **antisense** to specific mRNA oligonucleotides that mediate the expression of genetic information concerning GABAA and **glutamate** **receptor** subunits may become valuable tools in psychiatric research. Perhaps in the future these studies might generate new ideas useful in the therapy of genetically determined psychiatric illness.

16/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06953708 92076443

Cellular distribution of L-**glutamate** decarboxylase (GAD) and gamma-aminobutyric acid (GABAA) **receptor** mRNAs in the rat retina.

Brecha NC; Sternini C; Humphrey MF
Department of Medicine, UCLA 90024.

Cell Mol Neurobiol (UNITED STATES) Oct 1991, 11 (5) p497-509, ISSN 0272-4340 Journal Code: CPX
Contract/Grant No.: EY 04067, EY, NEI; DK 38752, DK, NIDDK; DK 40469, DK, NIDDK
Languages: ENGLISH
Document type: JOURNAL ARTICLE

1. Gamma-aminobutryic acid (**GABA**), a major inhibitory transmitter of the vertebrate retina, is synthesized from **glutamate** by L-**glutamate** decarboxylase (GAD) and mediates neuronal inhibition at GABAA receptors. GAD consists of two distinct molecular forms, GAD65 and GAD67, which have similar distribution patterns in the nervous system (Feldblum et al., 1990; Erlander and Tobin, 1991). GABAA receptors are composed of several distinct polypeptide subunits, of which the GABAA alpha 1 variant has a particularly extensive and widespread distribution in the nervous system. The aim of this study was to determine the cellular localization patterns of GAD and GABAA alpha 1 **receptor** mRNAs to define **GABA**- and GABAA **receptor**-synthesizing neurons in the rat retina. 2. GAD and GABAA alpha 1 mRNAs were localized in retinal neurons by in situ hybridization histochemistry with 35S-labeled **antisense** RNA probes complementary to GAD67 and GABAA alpha 1 mRNAs. 3. The majority of neurons expressing GAD67 mRNA is located in the proximal inner nuclear layer (INL) and ganglion cell layer (GCL). Occasional GAD67 mRNA-containing neurons are present in the inner plexiform layer. Labeled neurons are not found in the distal INL or in the outer nuclear layer (ONL). 4. GABAA alpha 1 mRNA is expressed by neurons distributed to all regions of the INL. Some discretely labeled cells are present in the GCL. Labeled cells are not observed in the ONL. 5. The distribution of GAD67 mRNA demonstrates that numerous amacrine cells (conventional, interstitial, and displaced) and perhaps interplexiform cells synthesize **GABA**. These cells are likely to employ **GABA** as a neurotransmitter. 6. The distribution of GABAA alpha 1 mRNA indicates that bipolar, amacrine, and perhaps ganglion cells express GABAA receptors having an alpha 1 polypeptide subunit, suggesting

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            150  S9
            286  S10
     S11     23  S9 AND S10
? rd
...completed examining records
     S12     15  RD (unique items)
? s s12 not s5
            15  S12
             6  S5
     S13     15  S12 NOT S5
? t s13/3,ab/all

 13/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09858743   98292485   PMID: 9628768
  Characterization of enhanced behavioral responses to L-DOPA following
repeated administration in the 6-hydroxydopamine-lesioned rat
model of Parkinson's disease.
  Henry B; Crossman A R; Brotchie J M
  Division of Neuroscience, School of Biological Sciences, University of
Manchester, 1.124 Stopford Building, Manchester, M13 9PT, United Kingdom.
  Experimental neurology (UNITED STATES) Jun 1998, 151 (2)
 p334-42, ISSN 0014-4886 Journal Code: 0370712
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Long-term treatment of Parkinson's disease with dopamine-replacing
agents such as L-3,4-dihydroxyphenylalanine (L-DOPA) is compromised by many
side-effects, most notably involuntary movements, L-DOPA-induced
dyskinesia. Acute challenge with dopamine-replacing drugs elicits a
rotational response in the 6-hydroxydopamine (6-OHDA)-lesioned
rat model of Parkinson 's disease. This rotation is
contraversive to the lesion and is considered to represent an
antiparkinsonian effect. More recently, it has become clear that the
rotational response shows plasticity and that repeated L-DOPA or
apomorphine therapy is accompanied by a marked enhancement in this
response. In this study, we demonstrate that the enhanced behavioral
response to repeated dopamine-replacement therapy seen in the 6-OHDA
-lesioned rat has pharmacological characteristics similar to L-DOPA-
induced dyskinesia seen in MPTP -lesioned primates and man.
Thus, the magnitude and rate of development of the enhanced response to
L-DOPA treatment is related to both the number of doses and the size of the
dose of L-DOPA administered. In contrast, de novo administration of
dopaminergic drugs that are associated with a lower incidence of
dyskinesia, e.g., bromocriptine or lisuride, does not lead to an enhanced
behavioral response following repeated treatment. However, following a
single "priming" administration of apomorphine, the rotational response
elicited by subsequent bromocriptine administrations is enhanced with
repeated treatment. Once established, the enhanced behavioral response to
repeated L-DOPA-administration (6.5 mg/kg, twice daily) can, like L-DOPA-
induced dyskinesia in man and MPTP -treated monkeys, be
selectively reduced by coadministration of L-DOPA with the
alpha2-adrenergic receptor antagonist yohimbine (10 mg/kg, -95%), the 5-HT
uptake inhibitor 5-MDOT (2 mg/kg, -90%), or the beta-adrenergic receptor
antagonist propranalol (10 mg/kg, -35%). While these rats do not exhibit
symptoms of dyskinesia per se, this rodent model does exhibit
behaviors, the underlying mechanism of which is likely to be similar to
that underlying L-DOPA-induced dyskinesia and may prove useful in
studying the molecular and cellular mechanisms of L-DOPA-induced
 dyskinesia in Parkinson's disease. Copyright 1998 Academic Press.
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13/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09102111 97022910 PMID: 8869270
Experimental **models** and behavioural tests used in the study of **Parkinson**'s disease.
Mokry J
Department of Histology and Embryology, Charles University Medical School, Hradec Kralove, Czech Republic.
Physiological research / Academia Scientiarum Bohemoslovaca (CZECH REPUBLIC) **1995**, 44 (3) p143-50, ISSN 0862-8408 Journal Code: 9112413
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The present review brings the survey of the most frequently used behavioural tests in experimental **models** of **Parkinson**'s disease (PD). Although there is no spontaneous occurrence of **parkinsonism** in **animals**, several experimental **animal models** of PD have been developed to achieve the same clinical features in **animals**. The techniques employing neurotoxins in lesioning the nigrostriatal dopaminergic (DA) system have a large selectivity and reproducibility. The most frequently used neurotoxins are 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**) and 6-hydroxydopamine (6-**OHDA**). **MPTP**-lesioned monkeys mimic best the symptomatology of PD in human patients while rats appear to be refractory to **MPTP**. For that reason, 6-**OHDA** is used to damage the substantia nigra in a **rodent model**. Behavioural tests of **animals** with nigrostriatal lesion represent valuable non-invasive methods for assessing the influence of damaged DA system on locomotor activity. The most frequently used experimental **model** of PD is the drug-evoked rotation in 6-**OHDA** unilaterally lesioned rats. This **model** produces well-defined and stable behavioural deficits. The rotation test is a useful parameter for evaluating imbalances of dopamine in both striata of the hemi-**parkinsonian rat model**. T-maze, treadmill running test or sensorimotor tests are used to evaluate spontaneous locomotor activity of lesioned **animals** . Skilled motor tasks measure the influence of dopamine-depleting lesions on complex motor acts. Transplantation of DA tissue into the striatum offers a new approach to the treatment of PD. Experimental **models** and behavioural tests are used to evaluate the extent of graft-**induced** recovery of **MPTP**- or 6-**OHDA** -lesioned **animals** . Different results obtained after the use of different tests reflect the level of graft integration into the host circuitry.

13/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08972152 96325519 PMID: 8714707
Chronic alterations in dopaminergic neurotransmission produce a persistent elevation of deltaFosB-like protein(s) in both the **rodent** and **primate** striatum.
Doucet J P; Nakabeppu Y; Bedard P J; Hope B T; Nestler E J; Jasmin B J; Chen J S; Iadarola M J; St-Jean M; Wigle N; Blanchet P; Grondin R; Robertson G S
Department of Pharmacology, University of Ottawa, Ottawa, Ontario, Canada K1H 8M5.
European journal of neuroscience (ENGLAND) Feb **1996**, 8 (2) p365-81, ISSN 0953-816X Journal Code: 8918110
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed
Using an antibody that recognizes the products of all known members of the fos family of immediate early genes, it was demonstrated that destruction of the nigrostriatal pathway by 6-hydroxydopamine (6-**OHDA**) lesions of the medial forebrain bundle produces a prolonged (>3 months) elevation of Fos-like immunoreactivity in the striatum. Using retrograde tract tracing techniques, we have previously shown that this increase in Fos-like immunoreactivity is located predominantly in striatal neurons that project to the globus pallidus. In the present study, Western blots were performed on nuclear extracts from the intact and denervated striatum of 6-**OHDA**-lesioned rats to determine the nature of Fos-immunoreactive protein(s) responsible for this increase. Approximately 6 weeks after the 6-**OHDA** lesion, expression of two Fos-related antigens with apparent molecular masses of 43 and 45 kDa was enhanced in the denervated striatum. Chronic haloperidol administration also selectively elevated expression of these Fos-related antigens, suggesting that their **induction** after dopaminergic denervation is mediated by reduced activation of D2-like dopamine receptors. Western blot immunostaining using an antibody which recognizes the N-terminus of FosB indicated that the 43 and 45 kDa Fos-related antigens **induced** by dopaminergic denervation and chronic haloperidol administration may be related to a truncated form of FosB known as deltaFosB. Consistent with this proposal, retrograde tracing experiments confirmed that deltaFosB-like immunoreactivity in the deafferented striatum was located predominantly in striatopallidal neurons. Gel shift experiments demonstrated that elevated AP-1 binding activity in denervated striata contained FosB-like protein(s), suggesting that enhanced deltaFosB levels may mediate some of the effects of prolonged dopamine depletion on AP-1-regulated genes in striatopallidal neurons. In contrast, chronic administration of the D1-like receptor agonist CY 208243 to 6-**OHDA**-lesioned rats dramatically enhanced deltaFosB-like immunoreactivity in striatal neurons projecting to the substantia nigra. Western blot immunostaining revealed that deltaFosB and, to a lesser extent, FosB are elevated by chronic D1-like agonist administration. Both the quantitative reverse transcriptase-polymerase chain reaction and the ribonuclease protection assay demonstrated that deltafosB mRNA levels were substantially enhanced in the denervated striatum by chronic D1-like agonist administration. Lastly, we examined the effects of chronic administration ofD1-like and D2-like dopamine receptor agonists on striatal deltaFosB expression in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**) **primate model** of **Parkinson**'s disease. In monkeys rendered **Parkinsonian** by **MPTP**, there was a modest increase in deltaFosB-like protein(s), while the development of dyskinesia produced by chronic D1-like agonist administration was accompanied by large increases in DeltaFosB-like protein(s). In contrast, administration of the long-acting D2-like agonist cabergoline, which alleviated **Parkinsonian** symptoms without producing dyskinesia reduced deltaFosB levels to near normal. Taken together, these results demonstrate that chronic alterations in dopaminergic neurotransmission produce a persistent elevation of deltaFosB-like protein(s) in both the **rodent** and **primate** striatum.

13/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08734239 96085946 PMID: 8527000
The expression of proenkephalin and prodynorphin genes and the **induction** of c-fos gene by dopaminergic drugs are not altered in the straitum of **MPTP**-treated mice.
Ziolkowska B; Horn G; Kupsch A; Hollt V
Neuropeptide Research Department, Institute of Pharmacology, Polish Academy of Sciences, Krakow, Poland.
Journal of neural transmission. Parkinson's disease and dementia section (AUSTRIA) **1995**, 9 (2-3) p151-64, ISSN 0936-3076

Journal Code: 8914371
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The expression of proenkephalin (PENK), prodynorphin (PDYN) and c-fos genes was studied in the striatum of C57B1/6 mice treated with 1-methyl-4-phenyl-1,2,3,6,-tetrahydropyridine (**MPTP**), which are used as a **rodent model** of **Parkinson**'s disease (PD). Two weeks after systemic administration of **MPTP** (2 x 40 mg/kg, s.c. 18h apart), the lesion of the substantia nigra (SN) could be visualised by loss of the nigral tyrosine hydroxylase (TH) mRNA hybridization signal and by a 91% decrease in striatal dopamine levels. The levels of PENK and PDYN mRNAs were not significantly changed in the striatum of the lesioned mice, as compared to non-treated controls. The **induction** of the immediate early gene c-fos by the dopamine D2 receptor antagonist haloperidol was not altered, while the selective D1 receptor agonist SKF 38393 failed to **induce** c-fos in the striatum of **MPTP** -treated mice. These results are in contrast to the data concerning rats with the 6-hydroxydopamine (6-**OHDA**) lesion of the SN, which serve as another **rodent model** of PD. In the striata of 6-**OHDA**-lesioned rats, PENK gene is upregulated, PDYN gene is down-regulated and the **induction** of c-fos gene by D2 receptor antagonists is abolished, whereas selective D1 receptor agonists **induce** c-fos gene, which does not occur in non-lesioned rats. We presume that the lack of influence of the **MPTP** lesion in mice on the striatal gene expression was mainly caused by insufficient dopamine depletion in the striatum, which could not be increased in this **model**. The importance of the changes observed in 6-**OHDA**-lesioned rats has been discussed in the context of the **mouse** and **primate MPTP models** of PD.

13/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08699014 96033746 PMID: 7472415

In a **rat model** of **parkinsonism** , lesions of the subthalamic nucleus reverse increases of reaction time but **induce** a dramatic premature responding deficit.

Baunez C; Nieoullon A; Amalric M
Laboratoire de Neurobiologie Cellulaire et Fonctionnelle, CNRS, Marseille, France.

Journal of neuroscience : the official journal of the Society for Neuroscience (UNITED STATES) Oct **1995**, 15 (10) p6531-41, ISSN 0270-6474 Journal Code: 8102140
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Lesions of the subthalamic nucleus (STN) have been found to reduce the severe akinetic motor symptom produced in **animal models** of **Parkinson** 's disease, such as in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**) or in monoamine-depleted rats. However, little is known about the effect of STN exclusion on subtle motor deficits **induced** by moderate dopaminergic lesions in complex motor tasks. The present study was thus performed on rats trained in a reaction time (RT) task known to be extremely sensitive to variations of dopamine transmission in the striatum. **Animals** were trained to release a lever after the onset of a visual stimulus within a time limit to obtain a food reward. Discrete dopamine depletion produced by infusing the neurotoxin 6-hydroxydopamine (6-**OHDA**) bilaterally into the dorsal part of the striatum, produced motor initiation deficits which were revealed by an increase in the number of delayed responses (lever release after the time limit) and a lengthening of RTs. In contrast,

bilateral excitotoxic lesion of the STN with ibotenic acid **induced** severe behavioral deficits which were opposite to those produced by the dopaminergic lesion, as shown by an increase in the number of premature responses (lever release before the onset of the visual stimulus) and a decrease of RTs. Surprisingly, the performance of the **animals** bearing a double lesion (striatal dopaminergic lesion followed 14 d later by STN ibotenic lesion) was still impaired 40 d after the ibotenic lesion. As expected, the 6-**OHDA-induced** motor initiation deficits were reversed by a subsequent STN lesion. However, the dramatic increase of premature responses contributing to major behavioral deficits **induced** by the STN lesion remained unchanged. Thus, the bilateral lesion of the STN was found to alleviate the motor deficits in this **model** of **parkinsonism** , but essentially produced over time, long lasting deficits that might be related to dyskinesia or cognitive impairment. The present results strongly support the recent concept of a predominant control of the STN on basal ganglia output structures.

13/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08569380 95327796 PMID: 7604140

Selective dopamine antagonist pretreatment on the antiparkinsonian effects of benzazepine D1 dopamine agonists in **rodent** and **primate models** of **Parkinson**'s disease--the differential effects of D1 dopamine antagonists in the **primate**.

Gnanalingham K K; Hunter A J; Jenner P; Marsden C D

Parkinson's Disease Society Experimental Research Laboratories, King's College, London, UK.

Psychopharmacology (GERMANY) Feb **1995**, 117 (4) p403-12, ISSN 0033-3158 Journal Code: 7608025

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

In rats with unilateral 6-hydroxydopamine (6-**OHDA**) lesions of the medial forebrain bundle, pretreatment with the D1 DA antagonists, SCH 23390 (7-chloro-8-hydroxy-2,3,4,5-tetrahydro-3-methyl-1-phenyl-1H-3-benzazepin e) and A66359 (1- 2-bromo-4,5-dimethoxybenzyl]-7-hydroxy-6-methoxy-2-methyl-1,2,3,4 tetrahydroisoquinoline), but not the D2 DA antagonist raclopride inhibited the contralateral circling **induced** by the benzazepine D1 DA agonists SKF 38393 (7-H, 3-H analogue of SCH 23390), SKF 80723 (7-H, 3-H, 6-Br analogue) and SKF 83959 (7-H, 6-Cl, 3'-CH3 analogue). In **MPTP** (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) treated common marmosets, administration of SKF 80723 and SKF 83959 increased locomotor activity and reversed the motor disability. Grooming and oral activities were also increased. Pretreatment with SCH 23390 and A66359 inhibited all the behavioural changes **induced** by both D1 DA agonists. In general, higher doses of A66359 and more especially SCH 23390 were needed to inhibit SKF 83959 and SKF 80723 **induced** increases in oral activity and grooming than locomotor activity. Raclopride pretreatment did not affect SKF 83959 and SKF 80723 **induced** oral activity and grooming, though it reduced the duration of the locomotor changes **induced** by the D1 DA agonists. These findings demonstrate that the behavioural effects of benzazepine D1 DA agonists in the 6-**OHDA** lesioned **rat** and **MPTP** -treated marmoset are mediated by D1 DA receptor sites, although in the **primate**, stimulation of D2 DA receptors by endogenous DA may be necessary in facilitating the antiparkinsonian effects of D1 DA agonists. The differential sensitivities of locomotor/motor disability and oral/grooming behaviours to antagonism by D1 DA antagonists may indicate the involvement of multiple D1 DA receptor subtypes in mediating benzazepine D1 DA agonist **induced** behaviours in the **MPTP** -treated marmoset.

13/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08531765 95288444 PMID: 7770604
The differential behavioural effects of benzazepine D1 dopamine agonists with varying efficacies, co-administered with quinpirole in **primate** and **rodent models** of **Parkinson**'s disease.
Gnanalingham K K; Hunter A J; Jenner P; Marsden C D
Parkinson's Disease Society, Experimental Research Laboratories, King's College, London, U.K.
Psychopharmacology (GERMANY) Feb **1995**, 117 (3) p287-97, ISSN 0033-3158 Journal Code: 7608025
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The effects of co-administration of quinpirole with benzazepine D1 dopamine (DA) agonists possessing full/supramaximal (SKF 80723 and SKF 82958), partial (SKF 38393 and SKF 75670) and no efficacies (SKF 83959) in stimulating adenylate cyclase (AC) were investigated in **rodent** and **primate models** of **Parkinson**'s disease (PD). In rats with a unilateral 6-hydroxydopamine (6-**OHDA**) lesion of the medial forebrain bundle, co-administration of SKF 38393 (7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine), SKF 75670 (3-CH3 analogue), SKF 80723 (6-Br analogue), SKF 83959 (6-Cl, 3-CH3, 3'-CH3 analogue) and SKF 82958 (6-Cl, 3-C3H5 analogue) strongly potentiated the contralateral circling **induced** by quinpirole. In **MPTP** (1-methyl-4-phenyl-1,2,3,6-tetra hydropyridine) treated common marmosets, administration of quinpirole alone increased locomotor activity and reversed motor deficits. Grooming and oral activity were unaltered. Co-administration of SKF 38393 and SKF 75670 inhibited the quinpirole-**induced** changes in locomotor activity and motor disability. The combined treatment of SKF 80723 or SKF 82958 with quinpirole had no overall effect on locomotor activity or motor disability. In contrast, SKF 83959 extended the duration of the quinpirole-**induced** increase in locomotor activity with corresponding decreases in motor disability. Co-administration of high doses of SKF 82958 and more especially SKF 83959 and SKF 80723, with quinpirole **induced** hyperexcitability and seizures. Oral activity and grooming were unaltered following the co-administration of benzazepine derivatives with quinpirole. The ability of some benzazepine D1 DA agonists to prolong the antiparkinsonian effects of quinpirole in the **MPTP**-treated marmoset may indicate a role for certain D1 DA agonists in the clinical treatment of PD. In general, the behavioural responses to the combined administration of benzazepines with quinpirole in the 6-**OHDA** lesioned **rat** and more especially the **MPTP**-treated marmoset failed to correlate with their ability to stimulate AC. These observations further implicate a behavioural role for D1 DA receptors not linked to AC.

13/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07622110 93147822 PMID: 1491248
Synergism of NBQX with dopamine agonists in the 6-**OHDA rat model** of **Parkinson**'s disease.
Loschmann P A; Kunow M; Wachtel H
Research Laboratories, Schering AG, Berlin, Federal Republic of Germany.
Journal of neural transmission. Supplementum (AUSTRIA) **1992**, 38 p55-64, ISSN 0303-6995 Journal Code: 0425126
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Advance in understanding of the anatomy, physiology and pharmacology of basal ganglia organisation over the past decade revealed a functional relation between excitatory glutamatergic and the degenerated dopaminergic nigrostriatal transmitter systems which could serve as targets for pharmacological interventions in **Parkinson**'s disease. The selective AMPA-antagonist NBQX is not effective in **animal models** of **Parkinson**'s disease when given alone but ameliorates **parkinsonian** symptomatology and enhances the locomotor response of a threshold dose of L-DOPA. These synergistic effects are seen in the **MPTP** -treated (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) common marmoset and the **rat** with unilateral 6-hydroxydopamine (6-**OHDA**) lesions of the substantia nigra. Here we report that, in the latter **model** , such synergism of NBQX is also seen with the direct dopamine agonists lisuride and apomorphine, indicating the potential usefulness of AMPA antagonists for the symptomatic treatment of **Parkinson** 's disease.

13/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07619766 93125584 PMID: 8419792
The possible role of iron in the etiopathology of **Parkinson**'s disease.
Youdim M B; Ben-Shachar D; Riederer P
Department of Pharmacology, Bruce Rappaport Faculty of Medicine, Technion, Haifa, Israel.
Movement disorders : official journal of the Movement Disorder Society (UNITED STATES) **1993**, 8 (1) p1-12, ISSN 0885-3185
Journal Code: 8610688
Erratum in Mov Disord 1993 Apr;8(2) 255
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The identification of 6-hydroxydopamine (6-**OHDA**) and N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**) as dopaminergic neurotoxins that can **induce parkinsonism** in humans and **animals** has contributed to a better understanding of **Parkinson** 's disease (PD). Although the involvement of similar neurotoxins has been implicated in PD, the etiology of the disease remains obscure. However, the recently described pathology of PD supports the view for a state of oxidative stress in the substantia nigra (SN), resulting as a consequence of the selective accumulation of iron in SN zona compacta and within the melanized dopamine neurons. Whether iron is directly involved cannot be ascertained. Nevertheless, the biochemical changes due to oxidative stress resulting from tissue iron overload (siderosis) are similar to those now being identified in **parkinsonian** SN. These include the reduction of mitochondrial electron transport, complex I and III activities, glutathione peroxidase activity, glutathione (GSH) ascorbate, calcium-binding protein, and superoxide dismutase and increase of basal lipid peroxidation and deposition of iron. The participation of iron-**induced** oxygen free radicals in the process of nigrostriatal dopamine neuron degeneration is strengthened by recent studies in which the neurotoxicity of 6-**OHDA** has been linked to the release of iron from its binding sites in ferritin. This is further supported by experiments with the prototype iron chelator, desferrioxamine (Desferal), a free-radical inhibitor, which protects against 6-**OHDA**-**induced** lesions in the **rat** . Indeed, intranigral iron injection in rats produces a selective lesioning of dopamine neurons, resulting in a behavioral and biochemical **parkinsonism**.

13/3,AB/10 (Item 10 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

07562204 93086829 PMID: 1280793
NBQX (6-nitro-sulfamoyl-benzo-quinoxaline-dione) and CPP (3-carboxy-piperazin-propyl phosphonic acid) potentiate dopamine agonist **induced** rotations in substantia nigra lesioned rats.
Wachtel H; Kunow M; Loschmann P A
Research Laboratories of Schering AG, Berlin, FRG.
Neuroscience letters (NETHERLANDS) Aug 17 **1992**, 142 (2) p179-82, ISSN 0304-3940 Journal Code: 7600130
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Degeneration of dopaminergic nigrostriatal neurons in **primate models** of **Parkinson**'s disease (PD) leads to an overactivity of excitatory glutamatergic projections from the subthalamic nucleus (STN) to the output nuclei of the basal ganglia resulting in rigidity and akinesia. The selective alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) antagonist 6-nitro-sulfamoyl-benzo-quinoxaline-dione (NBQX) and the competitive N-methyl-D-aspartate (NMDA) antagonist 3-carboxy-piperazin-propyl phosphonic acid (CPP) ameliorate **parkinsonian** symptomatology when co-administered with threshold doses of L-DOPA in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**)-treated common marmosets and **induce** rotations in rats with unilateral 6-hydroxydopamine (6-**OHDA**) lesions of the substantia nigra (SN). Here we report that in the 6-**OHDA**-lesioned **rat** NBQX and CPP **induce** contralateral rotations when combined with threshold doses of the direct dopamine agonists lisuride or apomorphine. AMPA antagonists and competitive NMDA antagonists may therefore be suitable as adjuvants for the treatment of PD.

13/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06289139 89376009 PMID: 2528389
A 6-hydroxydopamine-**induced** selective **parkinsonian rat model**.
Perese D A; Ulman J; Viola J; Ewing S E; Bankiewicz K S
Surgical Neurology Branch, NINCDS, Bethesda, MD 20892.
Brain research (NETHERLANDS) Aug 14 **1989**, 494 (2) p285-93, ISSN 0006-8993 Journal Code: 0045503
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Previous **parkinsonian rat models** have generally been characterized by unilateral destruction of both the nigrostriatal pathway and the mesolimbic pathway using the neurotoxin 6-hydroxydopamine (6-**OHDA**). We created a hemiparkinsonian **model** in which there is 6-**OHDA-induced** destruction of the dopaminergic nigrostriatal pathway but sparing of the dopaminergic mesolimbic pathway. This resulted in reproducible, quantifiable rotational behavior in response to either amphetamine or apomorphine and a near total depletion of dopamine in the striatum ipsilateral to the lesion with a dorsolateral distribution of supersensitive dopaminergic D2 receptors. This **model** parallels the **MPTP** (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine)-**induced** hemiparkinsonian **model** in primates and more closely approximates the extent of neurodegeneration seen in human idiopathic **Parkinson**'s disease than previous **parkinsonian rat models**. It may therefore prove a convenient **model** for studying the recently reported phenomenon of sprouting from host dopaminergic neurons following tissue implantation.

13/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05858722 88281296 PMID: 3134931
Transplantation of the superior cervical ganglion into the brain--a new experimental therapy of **Parkinson** disease]
Itakura T; Kamei I; Nakai K; Nakai M; Naka Y; Nakakita K; Imai H; Komai N
Department of Neurological Surgery Wakayama Medical College, Japan.
No to shinkei. Brain and nerve (JAPAN) Mar **1988**, 40 (3) p285-90, ISSN 0006-8969 Journal Code: 0413550
Document type: Journal Article ; English Abstract
Languages: JAPANESE
Main Citation Owner: NLM
Record type: Completed
To supplement catecholamine deficit in the brain with **Parkinson** disease, we have aimed to transplant the superior cervical ganglion (SCG), which contains norepinephrine and dopamine, into the brain. 1. Transplantation of SCG into **rat** cerebral cortex SCG was transplanted into the same **rat** 's parietal cortex. Three weeks after the transplantation, catecholamine histofluorescence revealed many transplanted catecholamine cells in the cortex. However, no fibers extended from the transplanted tissue to the cerebral cortex. Some catecholamine fibers extended to the cerebral cortex where 6-**OHDA** (a specific neurotoxin to the catecholamine neuron) had been pretreated. 2. Transplantation of SCG into the caudate nucleus of **MPTP-induced Parkinson** monkey For **animal model** of **Parkinson** disease, **MPTP** (1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine) was administered to 5 monkeys. Tow weeks after **MPTP** administration, dopamine terminals disappeared in the caudate nucleus. After transplantation of SCG in the same **animal**, many transplanted SCG cells extended their axons to the caudate nucleus. The present results showed that transplanted SCG cells were well survived in the brain. Under a special circumstance such as shortage of catecholamine in the brain, transplanted SCG cells extended their axons into the brain. It is suggested that the transplantation of SCG can be a new therapy for **Parkinson** disease.

13/3,AB/13 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09640983 BIOSIS NO.: 199598095901
The role of excitatory amino acids in experimental **models** of **Parkinson**'s disease.
AUTHOR: Ossowska K
AUTHOR ADDRESS: Dep. Neuro-Psychopharmacol., Inst. Pharmacol., Polish Acad. Sci., 12 Smetna St., PL-31-343 Krakow**Poland
JOURNAL: Journal of Neural Transmission Parkinson's Disease and Dementia Section 8 (1-2):p39-71 **1994**
ISSN: 0936-3076
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The aim of this article was to review the recent literature on the role of excitatory amino acids in **Parkinson**'s disease and in **animal** equivalents of **parkinsonian** symptoms. Effects of NMDA and AMPA antagonists on the reserpine-**induced** akinesia, catalepsy and rigidity, on the neuroleptic-**induced** catalepsy, on the turning behaviour of 6-**OHDA**-lesioned rats, as well as on the **parkinsonian** symptoms evoked by **MPTP** in monkeys were analysed. Moreover, the role of NMDA antagonists in **Parkinson**'s

disease was discussed. Data concerning the protective influence of these drugs on degenerative properties of methamphetamine, **MPTP** and 6-OHDOPA were also presented. On the basis of the above findings, the following conclusions may be drawn: (1) disturbances in the glutamatergic transmission in various brain structures seem to play a significant role in the development of symptoms of **Parkinson**'s disease; (2) the NMDA-receptor blocking component may make a substantial contribution to the therapeutic effect of antiparkinsonian drugs; a similar contribution of AMPA-receptor blocking component has not been sufficiently documented, so far; (3) compounds blocking NMDA receptors may possibly prevent the development of **Parkinson**'s disease; this presumption needs, however further studies; (4) side effects of NMDA receptor antagonists may be a limiting factor in the use of these compounds in humans.

1994

13/3,AB/14 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08855802 BIOSIS NO.: 199396007303
Functional studies on monoaminergic transmitter release in **Parkinsonism**.
AUTHOR: Wesemann Wolfgang(a); Grote Christoph; Clement Hans-Willi; Block Frank; Sontag Karl-Heinz
AUTHOR ADDRESS: (a)Dep. Neurochemistry, Inst. Physiological Chemistry, Philipps Univ., Hans-Meerwein-Strasse, D-355**Germany
JOURNAL: Progress in Neuro-Psychopharmacology & Biological Psychiatry 17 (3):p487-499 **1993**
ISSN: 0278-5846
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In vivo pulse voltammetry and apomorphine **induced** circling behaviour were used to study the effect of antiparkinsonian drugs and neurotoxins on striatal, extraneuronal dihydroxyphenylacetic acid (DOPAC) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations which are a measure of dopamine (DA) release/DA metabolism and serotonin (5-HT) release, respectively. The DA precursor dihydroxyphenylalanine (DOPA, i.p.) increased extraneuronal DOPAC and reduced 5-HIAA levels whereas the opposite effect was **induced** by the 5-HT precursor 5-hydroxytryptophan (5-HTP, i.p.). Tryptophan, i.p., decreased the extraneuronal DOPAC levels without significant effect on 5-HT release. The monoamine oxidase (MAO) inhibitors pargyline, i.p., and deprenyl, i.p., as well as the DA agonist haloperidol, i.p., decreased the catechol signal. The DA antagonist haloperidol, i.p., increased extraneuronal DOPAC. In longterm studies unilateral application of the neurotoxins 6-hydroxydopamine (6-**OHDA**), 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**), and 1-methyl-4-phenylpyridiniumcation (MPP+) into the substantia nigra pars compacta abolished the DOPAC signal in the striatum at the lesioned side. This effect can be partially or fully restored by DOPAC depending on the time elapsed after neurotoxin administration. In accordance with the voltammetric recorded unilateral lesion of the dopaminergic system the apomorphine stimulated circling behaviour was significantly enhanced in **MPTP** and MPP+ treated rats as compared with controls. The results obtained indicate that antiparkinsonian drugs and neurotoxins besides their effect on total catecholamine and 5-HT concentrations change specifically the extraneuronal levels of the transmitter (metabolites). Moreover the results suggest that neurotoxin-treated rats can be used as a **model** to study **Parkinson**-like effects with regard to the pathogenesis and treatment of this disease.

1993

13/3,AB/15 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08405418 BIOSIS NO.: 000094123072
NBQX 6 NITROSULFAMOYLBENZOQUINOXALINEDIONE AND CPP 3 CARBOXYPIPERAZINEPROPYLPHOSPHONIC ACID POTENTIATE DOPAMINE AGONIST **INDUCED** ROTATIONS IN SUBSTANTIA NIGRA LESIONED RATS
AUTHOR: WACHTEL H; KUNOW M; LOESCHMANN P-A
AUTHOR ADDRESS: SCHERING AG, DEP. NEUROPSYCHOPHARMACOL., POSTFACH 65 03 11, D-1000 BERLIN 65, GERMANY.
JOURNAL: NEUROSCI LETT 142 (2). 1992. 179-182. **1992**
FULL JOURNAL NAME: Neuroscience Letters
CODEN: NELED
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Degeneration of dopaminergic nigrostriatal neurons in **primate models** of **Parkinson**'s disease (PD) leads to an overactivity of excitatory glutamatergic projection from the subthalamic nucleus (STN) to the output nuclei of the basal ganglia resulting in rigidity and akinesia. The selective .alpha.-amino-3-hydroxy-5-methyl-4-isoxazolepropionate (AMPA) antagonist 6-nitro-sulfamoyl-benzo-quinoxaline-dione (NBQX) and the competitive N-methyl-D-aspartate (NMDA) antagonist 3-carboxy-piperazin-propyl phosphonic acid (CPP) ameliorate **parkinsonian** symptomatology when coadministered with threshold doses of L-DOPA in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (**MPTP**)-treated common marmosets and **induce** rotations in rats with unilateral 6-hydroxydopamine (6-**OHDA**) lesions of the substantia nigra (SN). Here we report that in the 6-**OHDA**-lesioned **rat** NBQX and CPP **induce** contralateral rotations when combined with threshold doses of the direct dopamine agonists lisuride or apomorphine. AMPA antagonists and competitive NMDA antagonists may therefore be suitable as adjuvants for the treatment of PD.

1992
? ds

Set	Items	Description
S1	7575	PARKINS? AND MODEL?
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S9	150	S8 AND OHDA
S10	286	S8 AND MPTP
S11	23	S9 AND S10
S12	15	RD (unique items)
S13	15	S12 NOT S5

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        1593189  MODEL?
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             6  ANNIMAL?
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Processing
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         29890  GAD?
         21929126  PY<1999
     S4       9  S3 AND GAD? AND PY<1999
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...completed examining records
     S5       6  RD (unique items)
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 5/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09781969   98197141   PMID: 9527896
  Toxicity of dieldrin for dopaminergic neurons in mesencephalic cultures.
  Sanchez-Ramos J; Facca A; Basit A; Song S
  Department of Neurology, University of South Florida, James A. Haley VA
Medical Center, Research 151, 13000 Bruce B Downs Boulevard, Tampa, Florida
33612, USA.
  Experimental neurology (UNITED STATES) Apr 1998, 150 (2)
 p263-71, ISSN 0014-4886 Journal Code: 0370712
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Dieldrin can be retained for decades in lipid-rich tissue and has been
measured in some postmortem PD brains. Dieldrin has been reported to
deplete brain monoamines in several species and has been shown to inhibit
mitochondrial respiration. To further investigate the possibility that it
may be involved in the pathogenesis of parkinsonism, its toxicity for
dopaminergic (DA) neurons was assessed in a mesencephalic cell culture
model . Primary neuronal cultures of mesencephalic neurons were
prepared from fetal rats or fetal mice, grown for 1 week and incubated with
Dieldrin (0.01-100 microM) for 24 or 48 h. Toxicity for DA neurons was
determined by measuring density of surviving tyrosine hydroxylase
immunoreactive (TH-ir) cells. Toxicity for gamma-aminobutyric acid
(GABA)-ergic neurons was determined by measuring survival of glutamate
decarboxylase (GAD )-ir neurons. General, nonselective cytotoxicity
was determined by counting cells visualized by phase contrast microscopy or
by DAPI-stained cells with fluorescence microscopy. Dieldrin exposure for
24 h resulted in a dose-dependent decrease in survival of TH-IR cells (DA
neurons) with a 50% decrease (EC50) produced by 12 microM in rat
mesencephalic cultures. Dieldrin also produced a dose- and time-dependent
decrease in mouse DA-ergic and GABA-ergic neurons in mouse mesencephalic
cultures. GABA-ergic neurons were less sensitive to the toxin compared to
DA-ergic neurons. Cellular uptake of 3H-DA was also affected by lower
concentrations of Dieldrin (EC50 = 7.98 microM) than uptake of 3H-GABA
(EC50 = 43 microM). Thus, Dieldrin appears to be a relatively selective
DA-ergic neurotoxin in mesencephalic cultures. Dieldrin, which may be
ubiquitous in the environment, is proposed as an agent which can initiate
```

and promote dopaminergic neurodegeneration in susceptible individuals. Copyright 1998 Academic Press.

5/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09519041 97410058 PMID: 9266773
Glutamate decarboxylase (**GAD67** and **GAD65**) gene expression is increased in a subpopulation of neurons in the putamen of **Parkinsonian** monkeys.
Soghomonian J J; Laprade N
Centre de Recherche en Neurobiologie et Departement d'Anatomie, Faculte de Medecine, Universite Laval, Quebec, Canada. Jean-Jacques.Soghomonian@anm.ulaval.ca
Synapse (New York, N.Y.) (UNITED STATES) Oct **1997**, 27 (2) p122-32, ISSN 0887-4476 Journal Code: 8806914
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The cellular distribution of the mRNAs encoding for the two isoforms of glutamate decarboxylase, **GAD67** and **GAD65**, was analyzed by in situ hybridization histochemistry in the caudate nucleus and putamen of control and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated **parkinsonian** squirrel monkeys. On brain sections processed with a radioactive and a digoxigenin-labeled cRNA probe, the **GAD67** and **GAD65** mRNAs were colocalized in virtually all labeled neurons of the caudate nucleus and putamen, in both control and MPTP-treated monkeys. Furthermore, neurons labeled with the **GAD** cRNAs constituted at least 90% of all striatal neurons, as estimated on adjacent Nissl-stained sections. In the two groups of monkeys, double-labeling experiments using a combination of radioactive **GAD67** or **GAD65** and digoxigenin-labeled preproenkephalin (PPE) cRNA probes showed that roughly half of all neurons labeled with the **GAD** cRNAs were also labeled with the PPE cRNA probe. When compared to controls, **GAD67** and **GAD65** mRNA levels were higher in the putamen, and to a lesser extent in the caudate nucleus, of MPTP-treated monkeys. Further analysis of labeling at the cellular level in a dorsolateral sector of the putamen revealed that **GAD67** and **GAD65** mRNA levels in MPTP-treated monkeys were increased in PPE-labeled (presumed striato-pallidal) neurons but not in PPE-unlabeled (presumed striato-nigral) neurons. Our results demonstrate that most neurons in the caudate nucleus and putamen of squirrel monkeys contain the mRNAs encoding for the two **GAD** isoforms. In addition, the selective increase in **GAD** mRNA levels in PPE-labeled neurons provides further evidence that striato-pallidal GABAergic neurons are hyperactive in MPTP-treated **parkinsonian** monkeys.

5/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07616026 93137245 PMID: 8093682
An **animal model** for coexisting tardive dyskinesia and tardive **parkinsonism**: a glutamate hypothesis for tardive dyskinesia.
Gunne L M; Andren P E
Department of Psychiatry, Ulleraker, Uppsala University, Sweden.
Clinical neuropharmacology (UNITED STATES) Feb **1993**, 16 (1) p90-5, ISSN 0362-5664 Journal Code: 7607910
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
There is now ample evidence for long-term malfunctioning within five

different brain GABAergic pathways in a monkey **model** for tardive dyskinesia (TD). Three of these GABA connections (GPe-STN, CP-SNr, and CP-GPi) are chronically downregulated during neuroleptic treatment and after some years they do not seem to regain their normal activity, even when the neuroleptics are discontinued. The persistent downregulation of these three GABA connections, evidenced by depressions of terminal **GAD** activity and GABA levels, appears to be a conceivable mechanism behind tardive **parkinsonism** (TP), often reported to coexist with TD in the clinic. The TD patients' well-known lack of awareness of their symptoms may be due to their **parkinsonian** "sensory neglect." Another two GABA malfunctioning connections were found in our monkey **model**: SNr-VA/VL and GPi-VA/VL. These pathways are upregulated during chronic neuroleptic treatment, partly due to an elevated glutamate release within subthalamofugal pathways. This chronic glutamatergic hyperactivity may have acted via an excitotoxic mechanism and consequently both GPi and VA/VL had a low synaptic activity in our dyskinetic monkeys, as measured by 2-deoxyglucose uptake, even 4 months after the last neuroleptic dose. It is hypothesized that TD may be due to an excitotoxic lesion of the inhibitory GABAergic VA/VL afferents, while TP has to do with persistent malfunctioning of downregulated SNr and GPi afferents.

5/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04178304 83163228 PMID: 6131932
Striatal GABAergic neuronal activity is not reduced in **Parkinson**'s disease.
Perry T L; Javoy-Agid F; Agid Y; Fibiger H C
Journal of neurochemistry (UNITED STATES) Apr **1983**, 40 (4) p1120-3, ISSN 0022-3042 Journal Code: 2985190R
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The content of gamma-aminobutyric acid (GABA) and the activities of glutamic acid decarboxylase (**GAD**) and tyrosine hydroxylase (TH) were measured in whole putamen obtained at autopsy from 13 patients dying with idiopathic **Parkinson** 's disease and 13 appropriate control subjects. Mean GABA content was significantly elevated (by 28%) in the putamen of the **Parkinson**'s disease patients. TH activity was markedly reduced, while there was no significant reduction of **GAD** activity in the putamen of these patients. GABA content was also measured in both sides of the striatum in rats which had received unilateral injections of 6-hydroxydopamine (6-OHDA) in the vicinity of the axons of the nigrostriatal projection. Mean GABA content was found significantly elevated (by 33%) in the ipsilateral striatum. Loss of dopaminergic nigrostriatal neurons, in both human **Parkinson**'s disease and in the rat 6-OHDA **model**, is accompanied by increased striatal GABA content. The assumption that GABAergic neurotransmission is reduced in the striatum in **Parkinson**'s disease may not be correct.

5/3,AB/5 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11732615 BIOSIS NO.: 199800514346
Novel synthesis and release of GABA in cerebellar granule cell cultures after infection with defective herpes simplex virus vectors expressing glutamic acid decarboxylase.
AUTHOR: New Kent C; Gale Karen; Martuza Robert L; Rabkin Samuel D(a)
AUTHOR ADDRESS: (a)Dep. Microbiol., Georgetown Univ. Medical Cent., 3970 Reservoir Road NW, Washington, DC 20007**USA

JOURNAL: Molecular Brain Research 61 (1-2):p121-135 Oct. 30, **1998**
ISSN: 0169-328X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The inhibitory amino acid neurotransmitter gamma-aminobutyric acid (GABA) is synthesized from glutamate in a single step by the enzyme glutamatic acid decarboxylase (**GAD**). We sought to determine whether viral vectors containing **GAD** cDNA could be used to enhance synthesis and stimulation-evoked release of GABA in cultures of CNS neurons. For this purpose, we generated double-cassette defective herpes simplex virus (HSV) vectors that expressed one of the two **GAD** isoforms (**GAD65** or **GAD67**), and Escherichia coli LacZ. Infection of cerebellar granule cell (CGC) cultures with vectors containing **GAD** cDNA resulted in a significant increase in isoform-specific expression of **GAD**, synthesis of GABA, and stimulation-evoked GABA release. **GAD65** and **GAD67** vector-infected neurons exhibited a comparable profile of GABA levels, synthesis and release, as well as **GAD** protein distribution. In CGCs cultured for 6 days in vitro (DIV), GABA synthesized after vector-derived **GAD** expression was released by treatment with glutamate or veratridine, but only in a Ca2+-independent fashion. In more mature (10 DIV) cultures, both Ca2+-dependent, K+ depolarization-induced, as well as Ca2+-independent, veratridine-induced, GABA release was significantly enhanced by **GAD** vector infection. Treatment of CGCs with kainic acid, which destroys most of the GABAergic neurons (< 1% remaining), did not prevent vector-derived expression of **GAD** nor synthesis of GABA. This suggests that defective HSV vector-derived **GAD** expression can be used to increase GABA synthesis and release in CNS tissue, even in the relative absence of GABAergic neurons. The use of such **GAD** vectors in the CNS has potential therapeutic value in neurologic disorders such as epilepsy, chronic pain, **Parkinson**'s and Huntington's disease.

1998

5/3,AB/6 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03965451 BIOSIS NO.: 000076051017
STRIATAL GAMMA AMINO BUTYRIC-ACID-ERGIC NEURONAL ACTIVITY IS NOT REDUCED IN **PARKINSON** DISEASE
AUTHOR: PERRY T L; JAVOY-AGID F; AGID Y; FIBIGER H C
AUTHOR ADDRESS: DEP. PHARMACOL., UNIV. BRITISH COLUMBIA, VANCOUVER V6T 1W5, CANADA.
JOURNAL: J NEUROCHEM 40 (4). 1983. 1120-1123. **1983**
FULL JOURNAL NAME: Journal of Neurochemistry
CODEN: JONRA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The content of GABA and the activities of glutamic acid decarboxylase (**GAD**) and tyrosine hydroxylase (TH) were measured in whole putamen obtained at autopsy from 13 patients dying with idiopathic **Parkinson**'s disease and 13 appropriate control subjects. Mean GABA content was significantly elevated (by 28%) in the putamen of the **Parkinson**'s disease patients. TH activity was markedly reduced, while there was no significant reduction of **GAD** activity in the putamen of these patients. GABA content was also measured in both sides of the striatum in rats which had received unilateral injections of 6-hydroxydopamine (6-OHDA) in the vicinity of the axons of the nigrostriatal projection. Mean GABA content was found significantly

elevated (by 33%) in the ipsilateral striatum. Loss of dopaminergic nigrostriatal neurons, in both human **Parkinson**'s disease and in the rat 6-OHDA **model**, is accompanied by increased striatal GABA content. The assumption that GABAergic neurotransmission is reduced in the striatum in **Parkinson**'s disease may not be correct.

1983

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? ds

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PLEASE ENTER A COMMAND OR BE LOGGED OFF IN 5 MINUTES
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S5           6   RD (unique items)
S6        4046   S3 AND PY<1999
S7        2028   S6 AND (PRIMATE OR MOUSE OR MURINE OR RAT OR RODENT)
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            6007  OHDA
       S9    150  S8 AND OHDA
? s s8 and mptp
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            5685  MPTP
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